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PATENT 10/7/99  
Attorney Docket No. 8636

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Gelfand et al.

Serial No.: 07/873,897

Art Unit: 1651

Filed: April 24, 1992

Examiner: D. Naff

For: PURIFIED THERMOSTABLE ENZYME

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**SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 C.F.R. §1.56 and §1.97**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Attorneys for Applicants submit this Second Supplemental Information Disclosure Statement to bring to the Examiner's attention the references listed on the attached revised form PTO 1449 entitled "List of References Cited by Applicant,"<sup>1</sup> copies of which references are being submitted herewith, as well as certain papers and expert declarations filed during proceedings in foreign jurisdictions concerning counterparts of the captioned application, and certain inequitable conduct allegations made during the litigation of a patent related to the captioned application.

<sup>1</sup> Identification of the listed references is not to be construed an admission of Applicants or Attorneys for Applicants that such references are available as "prior art" against the subject application. Consequently, Applicants respectfully decline to use form PTO-1449, since this form identifies all of the references cited therein as "Prior Art". As an alternative, Applicants submit herewith a "revised form PTO 1449" entitled "List of References Cited" instead of "List of Prior Art Cited".

The references listed on the accompanying List of References Cited were brought to Applicants' attention in proceedings in Australia, Europe and Japan concerning foreign counterparts of the captioned application. During these proceedings, many of these references were alleged to be relevant to claims similar to those pending in the present application. These references have been reviewed and, for the reasons discussed in detail below, it is believed that these references fall outside the scope of material information for which there is a duty of disclosure under 37 C.F.R. § 1.56, because these references are either cumulative to, or are less relevant than, the references already of record in the captioned application. Nevertheless, because there is a likelihood that any patent issuing on the above-captioned application will be asserted against infringers, and because there is almost a certainty that accused infringers in patent litigations will raise all possible inequitable conduct allegations, no matter how flimsy, the Assignee and Applicants wish to bring the enclosed materials to the attention of the Patent and Trademark Office.

During the lengthy appeal of this case, the Assignee and some of the Applicants of the captioned application have been engaged in defending inequitable conduct allegations that have been made in the litigation of United States patent No. 4,889,818 (the "'818 patent"),<sup>2</sup> which issued from application Serial No. 07/069,509, filed June 17, 1987, of which the

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<sup>2</sup> The litigation is currently pending in the Northern District of California, *Hoffmann-LaRoche Inc. and Roche Molecular Systems, Inc. v. Promega Corporation*, Civil Action No. C-93-1748 VRW ("Roche v. Promega '818 Patent Litigation"). The parties are presently awaiting a decision of the Court after a trial on inequitable conduct which took place in February, 1999.

grandparent of the captioned application is a continuation-in-part application.<sup>3</sup> The claims of the '818 patent relate to a purified, thermostable DNA polymerase from *Thermus aquaticus*, both the native and recombinant forms. The inequitable conduct allegations against the '818 patent, which are fully discussed in materials submitted herewith (see, *infra* at page 7) are not believed to be relevant to the patentability of the subject matter claimed in the instant application.

Having had the experience in the litigation of the '818 patent of being subjected to numerous, spurious inequitable conduct allegations, it is out of an abundance of caution and desire to foreclose any allegations that Applicants or their representatives, in any way, intended to withhold material information from the Patent Office, that Applicants and their Assignee respectfully request that the references cited herein, which are not believed to be material, be made of record in the captioned application.

In Information Disclosure Statements filed in the present application and its parent, Serial No. 07/387,003, Applicants brought to the Examiner's attention, *inter alia*, references relating to thermostable polymerase compositions, including compositions containing stabilizers other than non-ionic detergents, such as gelatin and BSA.<sup>4</sup> Additionally, the Examiner cited and rejected claims over references disclosing non-thermostable reverse

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<sup>3</sup> The present application is a file wrapper continuation of application Serial No. 07/387,003, filed July 28, 1989, which is a divisional of application Serial No. 07/143,441, filed January 12, 1988, which is a continuation-in-part of application Serial No., 07/063,509, filed June 17, 1987, which issued as the '818 patent.

<sup>4</sup> See the Information Disclosure Statements Under 37 C.F.R. §§ 1.56, 1.97 and 1.98 filed on May 7, 1990 in parent application Serial No. 07/387,003 and on July 24, 1992 in the present application.

transcriptases, the purification of which involves buffers containing non-ionic detergents.<sup>5</sup>

Applicants also brought to the Examiner's attention a reference relating to non-thermostable reverse transcriptases (Wu and Cetta, 1975, *Biochemistry* 14:789-795 ("Wu and Cetta")).<sup>6</sup> In the Amendment dated January 15, 1993 in the present application, Applicants pointed out that Wu and Cetta discloses that non-ionic detergents stimulate the activity of viral reverse transcriptase but that non-ionic detergents had no effect on the activity of three mammalian cellular reverse transcriptases or a purified, bacterial reverse transcriptase, effectively teaching away from the present invention.

All of the references cited herein are believed to be either cumulative to, or less relevant than, the references cited either by Applicants or by the Examiner earlier during the prosecution of the present application. Specifically, the following references are believed to be cumulative to the references cited by Applicants and the Examiner relating to non-thermostable reverse transcriptases:

Ohno et al. (1977) Purification and characterization of the DNA polymerase of human breast cancer particles. *Proc. Natl. Acad. Sci. USA* 74:764-768;

Verma and Baltimore (1974) Purification of the RNA-Directed DNA Polymerase from Avian Myeloblastosis Virus and Its Assay with Polynucleotide Templates. *Methods in Enzymology* 24:124;

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<sup>5</sup> See the Office Action dated September 4, 1990, in parent application Serial No. 07/387,003 and accompanying PTO form 892, and Office Action dated July 15, 1992 of the present application.

<sup>6</sup> See Supplemental Information Disclosure Statement Under 37 C.F.R. §§ 1.56, 1.97, and 1.98, dated January 15, 1993, filed in the present application.

Ghosh et al. (1980) Determination of RNA Sequences by Primer Directed Synthesis and Sequencing of their cDNA Transcripts. *Methods in Enzymology* 65:59; and

Faras et al. (1972) Purification and Characterization of the Deoxyribonucleic Acid Polymerase Associated with Rous Sarcoma Virus. *Biochemistry* 11:2334-2342.

(Cited as references AP, BZ, CI, and CK, respectively, on the accompanying List of References Cited). These references, like certain of the references cited by the Examiner during prosecution (for example, Feller et al. (U.S. patent No. 4,409,200), Spiegelman (U.S. patent No. 4,379,839), and Goff et al. ( U.S. patent No. 4,943,531)), relate to non-thermostable reverse transcriptases which, at some point during their purification, are in buffers containing non-ionic detergents. It is believed that none of references AP, BZ, CI or CK provide any new, relevant information not already found in the references of record in the present application.

The other references listed on the accompanying List of References Cited are believed to be less relevant than the references already of record in the present application because they provide either very general background information or relate to compositions of proteins containing non-ionic detergents that are not even polymerase enzymes, much less thermostable polymerase enzymes. Since the Examiner has considered what is believed to be much closer prior art, it is believed that these other references are not material to the patentability of the claims of the present application. However, for the reasons discussed above, Applicants and their Assignee respectfully request that the cited references be made of record in the file history of the application.

Also in an abundance of caution, Applicants hereby bring to the Examiner's attention the documents listed below (copies of which are submitted herewith) which have been

filed by Opponents in Opposition proceedings in European and Australian counterparts of the captioned application:

1. Request for Opposition of European Patent No. EP-B-0 258 017 by Bioline Limited;
2. Request for Opposition of European Patent No. EP-B-0 258 017 by Promega Corporation;
3. Declaration of Professor Emeritus Arthur Kornberg from European Opposition Proceedings;
4. Declaration of Dr. Randall Dimond from European Opposition Proceedings;
5. Affidavit of David James Kemp from Australian Proceedings (see particularly §§ 6.28-6.31 and 12);
6. Affidavit of Bruce Ernest Kemp from Australian Proceedings (see particularly § 4);
7. Affidavit of Lynn Dalgarno from Australian Proceedings (see particularly §§ 4.15-4.20 and 9);
8. Affidavit of Stephen Donald Wilton from Australian Proceedings (see particularly § 12.24-12.26);
9. Declaration of Randall Dimond from Australian Proceedings;
10. Declaration of Ira Shildkraut from Australian Proceedings;
11. Declaration of Arthur Kornberg from Australian Proceedings;
12. Declaration of Richard Roberts from Australian Proceedings;
13. Declaration of Robert Scopes from Australian Proceedings (signed September 2, 1993);

14. Declaration of Robert Scopes from Australian Proceedings (signed February 9, 1996) (see particularly pages 56-67); and
15. Declaration of Nicholas Dixon from Australian Proceedings.

It is believed that the materials listed above do not raise issues that have not already been considered during the lengthy prosecution of the captioned application.<sup>7</sup> However, for the reasons discussed above with respect to the references cited herein, Applicants and their Assignee desire to make these materials of record in the file history of the present application.

In addition, as discussed briefly above, Applicants also bring to the Examiner's attention that allegations of inequitable conduct have been raised during the Roche v. Promega '818 Patent Litigation. Applicants provide herewith copies of the pre-trial and post-trial briefs from a bench trial on the issue of inequitable in the Roche v. Promega '818 Patent Litigation held in February 1999, which briefs summarize Promega's inequitable conduct allegations and Roche's response to these allegations. Due to the significant volume of documents, Applicants have not submitted the entire record from the trial or any Exhibits to the briefs nor Summary Judgment papers also relating to the issue of inequitable conduct. The Examiner is invited to contact Applicants if he would like any additional information or documentation. To date, a decision has not been issued by the Court. It is believed that Promega Corporation's allegations

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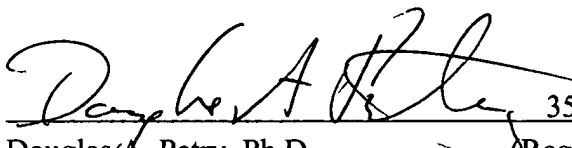
<sup>7</sup> Additionally, in a telephone conversation with the undersigned, the Examiner indicated that he did not believe such papers and expert declarations filed in foreign proceedings were relevant to the patentability of U.S. counterpart applications.

of inequitable conduct are baseless, and, in addition, relate to alleged misrepresentations and omissions that are not relevant to the patentability of the claims of the captioned application.<sup>8</sup>

Accordingly, even though it is believed that there is no duty under 37 C.F.R. § 1.56 to bring any of the information, references and documents discussed herein to the Examiner's attention, for the reasons discussed above, Applicants hereby request that the information provided above be made of record in the captioned application.

Respectfully submitted,

Date: October 1, 1999

  
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Enclosures

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<sup>8</sup> The Examiner also indicated to the undersigned that such inequitable conduct allegations were not relevant to the patentability of the captioned application.

## LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

APPLICATION NO.

07/873,897

APPLICANT

Gelfand et al.

FILING DATE

April 24, 1992

GROUP

1651

## U.S. PATENT DOCUMENTS

*EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
AA	4,457,916	1984	Hayashi et al.			

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	AB	JPO 86/251986	1986	Japan				
	AC	EP 166,529	1986	Europe				
	AD	WO 83/00288	1983	PCT				
	AE	JPO 5110487	1976	Japan				
	AF	JPO 60224499	1985	Japan				
	AG	JPO 60160884	1985	Japan				

## OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	AH	Bell et al. (1979) Purification and amino acid compositions of the structural proteins of Sindbis virus. <i>Virology</i> 97:287-294.
	AI	Burgess et al. (1977) Purification and properties of colony-stimulating factor from mouse lung-conditioned medium. <i>J Biol Chem</i> 252:1998-2003.
	AJ	Dalgarno et al. (1984) Characterization of Barmah Forest Virus: an alphavirus with some unusual properties. <i>Virology</i> 133:416-426.
	AK	Haeckel (1976) The reliability of a mechanized procedure (Perkin-Elmer C4) for the enzymatic determination of uric acid according to Kageyama. <i>J Clin Chem Clin Biochem</i> 14:165-171.
	AL	Husby et al. (1985) Increased non-specific binding of heat-treated proteins to plastic surfaces analyzed by ELISA and HPLC-fractionation. <i>J Immunoassay</i> 6:95-110.
	AM	Landi et al. (1975) "The multi-facets of tuberculin standardization" in <u>International WHO-IABS Symposium on Standardization and Control of Allergens Administered to Man, Geneva</u> , Develop Biol Standard 29:393-411.
	AN	Livesey and Donald (1982) Prevention of adsorption losses during radioimmunoassay of polypeptide hormones: effectiveness of albumins, gelatin, caseins, Tween 20 and plasma. <i>Clinica Chimica Acta</i> 123:193-198.
	AO	<u>McCutcheon's Emulsifiers and Detergents: 1983 North American Edition</u> , MC Publishing Co., Glen Rock, New Jersey, pp. 295-298.
	AP	Ohno et al. (1977) Purification and characterization of the DNA polymerase of human breast cancer particles. <i>Proc Natl Acad Sci USA</i> 74:764-768.
	AQ	Pearson et al. (1982) Myosin light chain kinase binding to plastic. <i>FEBS Letters</i> 145:327-331.
	AR	Pirrota and Bickle (1980) General purification schemes for restriction endonucleases. <i>Methods Enzymol</i> 65:89-95.
	AS	Smith et al. (1978) Elimination of nonspecific adsorption of serum proteins by sepharose-bound antigens. <i>Anal Biochem</i> 87:299-305.
	AT	Stralfors and Belfrage (1982) Properties and purification of the catalytic subunit of cyclic AMP-dependent protein kinase of adipose tissue. <i>Biochim Biophys Acta</i> 721:434-440.

AU	Suelter (1983) "Protein Structure and Stability" in <i>A Practical Guide to Enzymology</i> , Meister (ed), John Wiley & Sons, New York, pp. 1-26, 58-63, AND 124-132.
AV	Sugden et al. (1976) Purification and characterization of the catalytic subunit of adenosine 3':5'-cyclic monophosphate-dependent protein kinase from bovine liver. <i>Biochem J</i> 159:409-422.
AW	Tandon and Horowitz (1987) Detergent-assisted Refolding of Guanidinium Chloride-denatured Rhodanese. The effects of the Concentration and Type of Detergent. <i>J. Biol. Chem</i> 262:4486-91.
AX	Tandon and Horowitz (1986) Detergent-assisted Refolding of Guanidinium Chloride-denatured Rhodanese. The Effects of Lauryl Maltoside. <i>J. Biol. Chem.</i> 261:15615-8.
AY	Markovic-Housley and Garavito (1986) Effect of Temperature and Low pH on Structure and Stability of Matrix Porin in Micellar Detergent Solutions. <i>Biochim. Biophys Acta</i> , 869:158-70.
AZ	Wagner and Gray (1985) Effects of Detergent on Substrate Binding and Spin State of Purified Liver Microsomal Cytochrome P-450(LM2) from Phenobarbital-treated rabbits. <i>Biochemistry</i> 24:3809-14.
BA	Webber and Whiteley (1985) Comparative Activity of Rat Liver Dihydrofolate Reductase with 7,8-dihydrofolate and other 7,8-dihydropteridines. <i>Arch. Biochem Biophys</i> 236:681-90.
BB	Brunden et al. (1984) Dependence of the Conformation of a Colicin E1 Channel-forming Peptide on Acidic pH and Solvent Polarity. <i>J. Biol. Chem.</i> 259:7682-87.
BC	Muller and Roby (1984) Stabilization of Dextranuclease from <i>Leuconostoc mesenteroides</i> NRRL B-512F by Anionic Detergents, Polyethylene glycol and High-molecular-weight dextran. <i>Biochim. Biophys Acta</i> 785:89-96.
BD	Sawada et al. (1984) Purification and Characterization of Two Types of Trypsin-like Enzymes from Sperm of the Ascidian (Prochordata) <i>Halocynthia roretzi</i> . Evidence for the Presence of Spermosin, a novel Acrosin-like Enzyme. <i>J. Biol. Chem.</i> 259:2900-4.
BE	Grimshaw et al. (1984) Purification and Properties of 5,10 Methenyltetrahydrofolate Synthetase from <i>Lactobacillus casei</i> . <i>J. Biol. Chem.</i> 259:2728-33.
BF	Gavish (1983) Protection of Soluble Benzodiazepine Receptors from Heat Inactivation by GABAergic Ligands. <i>Life Sci.</i> 33:1479-83.
BG	Mozhaev and Martinek (1982) Inactivation and Reactivation of Proteins (enzymes). <i>Enzyme Microb. Tech.</i> 4:299-309.
BH	Ito and Kuriyama (1982) Some Properties of Solubilized GABA Receptor. <i>Brain Res.</i> 236:351-63.
BI	Stralfors and Belfrage (1982) Properties and Purification of the Catalytic Subunit of Cyclic AMP-dependent Protein Kinase of Adipose Tissue. <i>Biochim. Biophys Acta</i> 721:434-40.
BJ	Roach and Palmer (1981) Human Erythrocyte Cytosol Phosphatidyl-inositol-bisphosphate Phosphatase. <i>Biochim. Biophys Acta</i> 661:323-33.
BK	Porstmann et al. (1981) Temperature Dependent Rise in Activity of Horseradish Peroxidase Caused by Non-ionic Detergents and Its Use in Enzyme-Immunoassay. <i>Clin. Chim. Acta</i> 109:175-81
BL	Yang et al. (1981) Interferons, double-stranded RNA, and RNA degradation. Isolation and Characterization of Homogeneous Human (2'-5') $\alpha$ n Synthetase. <i>J. Biol. Chem.</i> 256:9324-8.
BM	Becht et al. (1980) Purification of Human Plasma Lipoprotein Lipase. <i>Biochim. Biophys Acta</i> 620:583-91.
BN	Muller-Esterl and Fritz (1980) Interactions of Boar Acrosin with Detergents. <i>Hoppe Seyler's Z. Physiol. Chem.</i> 361:1673-82.
BO	Rode et al. (1979) Purification of Mammalian Tumor (L 1210) Thymidylate Synthetase by Affinity Chromatography on Stable Biospecific Adsorbent. <i>J. Biol. Chem.</i> 254:11538-11543.
BP	Helenius et al. (1979) Properties of Detergents. <i>Meth in Enz.</i> 56:734-49.

BQ	Knudsen and Hubbell (1978) Stability of Rhodopsin in Detergent Solutions. <i>Membr. Biochem.</i> 1:297-322.
BR	Callahan et al. (1978) Sphingomyelinase in Human Tissues. IV. Purification of Sphingomyelinase from Human Placenta and Effect of Triton X-100. <i>Can. J. Biochem.</i> 56:885-91.
BS	Sedmak et al. (1978) Thermal and Vortical Stability of Purified Human Fibroblast Interferon. <i>Adv. Exp. Med Biol.</i> 110:133-52.
BT	Rizzolo and Tanford (1978) Behavior of Fragmented Calcium (II) Adenosine Triphosphatase from Sarcoplasmic Reticulum in Detergent Solution. <i>Biochem.</i> 17:4049-55.
BU	Mihara and Sato (1978) Detergent-Solubilized NADH-Cytochrome $b_5$ Reductase. <i>Meth. in Enz.</i> 52:102-108.
BV	Kaczorowski et al. (1978) Purification and Properties of D-Lactate Dehydrogenase from <i>Escherichia coli</i> ML 308-225. <i>Meth. in Enz.</i> 53:519-527.
BW	Yokoyama et al. (1977) Stabilization of Crystalline Acid Carboxypeptidase from <i>Penicillium janthinellum</i> by Nonionic Surfactants, and Inhibition of Enzyme Activity by Anionic Compounds. <i>Agric. Biol. Chem.</i> 41:1379-1383.
BX	Yamashita et al. (1975) Separation of 1-acylglycerolphosphate Acyltransferase and 1-acylglycerolphosphorylcholine Acyltransferase of Rat Liver Microsomes. <i>Proc. Natl. Acad. Sci. USA</i> 72:600-3.
BY	Helenius and Simons (1975) Solubilization of Membranes by Detergents. <i>Biochim. Biophys. Acta</i> 415:29-79.
BZ	Verma and Baltimore (1974) Purification of the RNA-Directed DNA Polymerase from Avian Myeloblastosis Virus and Its Assay with Polynucleotide Templates. <i>Meth. in Enz.</i> 24:125-130.
CA	Moses (1974) DNA Synthesis in Toluene-Treated Cells of <i>Escherichia coli</i> . <i>Meth. in Enz.</i> 24:219-224, 222.
CB	Takeda and Hizukuri (1972) Effect of Triton X-100 on Sweet Potato B-amylase. <i>Biochim. Biophys. Acta</i> 268:175-183.
CC	Gatt and Barenholz (1969) Sphingomyelinase from Rat Brain. <i>Meth. in Enz.</i> 14:144-152.
CD	Ernster (1967) DT Diaphorase. <i>Meth. in Enz.</i> 10:309-317.
CE	Wiedmer et al. (1979) Effects of Amphiphiles on Structure and Activity of Human Erythrocyte Membrane Acetylcholinesterase. <i>Eur. J. Biochem</i> 102:59-64.
CF	Lougheed et al. (1983) Physical Stability of Insulin Formulations. <i>Diabetes</i> 32:424-32.
CG	Sonoda and Tatibana (1983) Purification of N-acetyl-L-glutamate Synthetase from Rat Liver Mitochondria and Substrate and Activator Specificity on the Enzyme. <i>J. Biol. Chem.</i> 258:9839-44.
CH	Laskowski (1980) Purification and Properties of the Mung Bean Nuclease. <i>Methods in Enzymology</i> 65:268-276.
CI	Ghosh et al. (1980) Determination of RNA Sequences by Primer Directed Synthesis and Sequencing of their cDNA Transcripts. <i>Methods in Enzymology</i> 65:580-595.
CJ	Elises et al. (1986) Purification and Characterization of a UDP-Gal: $\beta$ -D-Gal(1,4)-D-GlcNAc $\alpha$ (1,3)-Galactosyl Transferase from Ehrlich Ascites Tumor Cells. <i>J. Biol. Chem.</i> 261:6064-6072.
CK	Faras et al. (1972) <i>Biochem</i> 11:2334-2342.

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.